REMARKS

FORMAL MATTERS:

Claims 5-8, 21-26 and 28-30 are cancelled without prejudice.

Claims 31-45 are newly added. Support for claims may be found in the specification and claims as originally filed, particularly at the following positions: page 6 lines 1-9; page 6, lines 20-21; page 11, lines 1-20; page 13, lines 12-18; page 15, lines 9-21; page 28, lines 18-19 and Table C on page 27. No new matter is added.

In view of the remarks set forth below, reconsideration of this application is respectfully requested.

INFORMATION DISCLOSURE STATEMENT

In compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2, and as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007), the Applicants wish to bring the Examiner's attention to the following co-pending U.S. application: 09/875,076.

The Examiner is asked to consider the above co-pending application as well as the file history of the same, which are available on the Patent Office's PAIR system.

REJECTION UNDER §101

Former claims 5-8, 21-26 and 28-30 were rejected under 35 U.S.C. § 101 as lacking patentable utility. Claims 5-8, 21-26 and 28-30 have been cancelled and, as such, this rejection is moot with respect to those claims. To the extent that the Examiner believes that this rejection can be applied to new claims 31-45, this rejection is respectfully traversed.

As noted in the Applicant's prior response, the instant specification discloses that the GPCR hARE-2 is selectively expressed in the *substantia nigra* - an area of the brain that degenerates in Parkinson's disease. The degeneration of the *substantia nigra* is the primary cause of Parkinson's disease and is accordingly indicative of disease progression.

The selective expression pattern of hARE-2 in cells of the *substantia nigra* allows for modulation of the intracellular levels of downstream signaling molecules (cAMP, IP_3 and/or Ca^{2+}) selectively in those cells. Fluctuation in the intracellular levels of these very same molecules is correlated with the viability of cells in the *substantia nigra*[1]. Thus, the claimed method can be used to identify compounds that modulate the intracellular levels of molecules that are directly implicated in the survival of those cells. Stated a different way, the claimed method can be used to identify compounds that increase the "well-being" of cells within the *substantia nigra*.

This utility requires no further research and is solidly grounded in well established biology, namely: 1) that GPCRs modulate the levels of intracellular signaling molecules; and 2) that the same GPCR-modulated intracellular signaling molecules affect the "well being" of *substantia nigra* cells (see, e.g., the references cited in footnote 1, below). In view of this well established biology and the Applicant's disclosure, the asserted utility would have been readily apparent at the time of filing to a person of ordinary skill in the art.

The utility is specific in that it can be assigned to a GPCR having expression in the *substantia nigra,* but not to the broader class of GPCRs. Applicants have identified a specific GPCR (hARE-2) and characterized its specific expression pattern, thus distinguishing hARE-2 from the broader class of GPCRs. Further, Applicants have disclosed a method for identifying candidate compounds as modulators of hARE-2 activity. Thus the utility is specific to the subject matter claimed (i.e. the utility of the claimed method would not be shared with the broader class of GPCRs but is specific to hARE-2). The utility is substantial in that the method has a current "real world" use in identifying candidate compounds that specifically modulate the activity of hARE-2. As described previously, such real world use includes identifying compounds which promote the viability of cells within the *substantia nigra*, the degeneration of which being the primary cause of Parkinson's disease, a disease which afflicts millions of people worldwide. Finally, the utility is credible in that a person of ordinary skill in the art would

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[1] See, e.g., Hulley et al, Inhibitors of type IV phosphodiesterases reduce the toxicity of MPTP in *substantia nigra* neurons *in vivo*. Eur. J. Neurosci. 1995 Dec 1;7(12):2431-40; and Hirsch et al, Neuronal vulnerability in Parkinson's disease. J. Neural Transm. Suppl. 1997;50:79-88, as discussed in prior response.

believe that the claimed method has utility based on the totality of evidence and reasoning provided. The claimed method employing hARE-2, disclosed by Applicants as a GPCR selectively expressed in the *substantia nigra*, finds utility *at least* on the basis of simply what would have been known about the *substantia nigra* and about GPCRs at the time of filing by a person of ordinary skill in the art. Accordingly, Applicants have satisfied all three prongs of the test outlined in the USPTO's Utility Guidelines.[2] Moreover, the Applicants submit that this use may be performed in the absence of further analysis of the hARE-2 protein or gene. As such, this utility is *not* an unacceptable "self-testing" utility described by *Brenner v. Manson*.[3]

While the Applicants believe that this asserted utility is sufficient to overcome this rejection, the claimed method has an additional utility. This additional utility is discussed below.

It is known that cells within the *substantia nigra* undergo extensive degeneration during Parkinson's disease (see, e.g., Damier et al Brain 1999 122: 1421-1436 and Damier et al 1999 Brain 122 1437-1448; references submitted in Information Disclosure Statement filed herewith). Since compounds identified using the claimed screening method would be expected to bind to cells that express hARE-2, those compounds can be employed in the study, diagnosis and/or monitoring of the *substantia nigra*, particularly in pathological conditions such as Parkinson's disease. For example, a compound identified using the claimed assay would be useful: a) in the analysis of a brain for disease-related changes in the architecture of the *substantia nigra*; b) in the evaluation of generalized cell damage versus cell type-specific damage in the *substantia nigra*; and c) as a marker for counting cells in the *substantia nigra* in order to provide an evaluation of disease severity. These additional utilities also exploit the selective expression of hARE-2 in *substantia nigra cells* and do not require that hARE-2 be specifically expressed in cells that die during Parkinson's disease. Since it is difficult to detect dead cells directly, tools for analyzing or visualizing living cells within the *substantia nigra* have a definite utility.

By way of example, the claimed method can be used to identify an antibody that specifically binds to hARE-2. Because hARE-2 is selectively expressed in cells of the *substantia nigra*, such an antibody can be labeled and used to study the *substantia nigra* of a diseased brain

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[2] Utility Examination Guidelines, *Federal Register* (Jan. 5, 2001) Vol. 66(4):1092-1099.

[3] *Brenner v. Manson* 86 S.Ct. 1033, 383 U.S. 519 (1966).

in the same way as others have used other compounds to study that area of the brain.[4] Since those other compounds have patentable utility, it follows that the claimed method, which can be used to identify antibodies that bind to hARE-2, should also have patentable utility.

These additional utilities are specific in that they can be assigned to a GPCR having expression in the *substantia nigra* but not to the broader class of GPCRs. Applicants have identified a specific GPCR (hARE-2) and characterized its specific expression pattern, thus distinguishing hARE-2 from the broader class of GPCRs. Further, Applicants have disclosed a method for identifying candidate compounds as modulators of hARE-2 activity. Thus these additional utilities are specific to the subject matter claimed (i.e. the utility of the claimed method would not be shared with the broader class of GPCRs but is specific to hARE-2). These additional utilities are substantial in that the method has a current "real world" use in identifying candidate compounds that specifically bind to and modulate the activity of hARE-2. As described previously, such real world use includes identifying compounds which can be employed in the study, diagnosis and/or monitoring of the *substantia nigra*, particularly in pathological conditions such as Parkinson's disease, a disease which afflicts millions of people worldwide. Finally, these additional utilities are credible in that a person of ordinary skill in the art would believe that the claimed method has utility based on the totality of evidence and reasoning provided. The claimed method employing hARE-2, disclosed by Applicants as a GPCR selectively expressed in the *substantia nigra*, finds utility *at least* on the basis of simply what would have been known about the *substantia nigra* and about GPCRs at the time of filing by a person of ordinary skill in the art. Accordingly, Applicants have satisfied all three prongs of the test outlined in the USPTO's Utility Guidelines.[5] Moreover, the Applicants submit that the above-described uses may be performed in the absence of further analysis of the hARE-2 protein or gene. As such, this utility is *not* an unacceptable "self-testing" utility described by *Brenner v. Manson*[6]

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[4] See, e.g., the Damier references cited in the accompanying Information Disclosure Statement.

[5] Utility Examination Guidelines, *Federal Register* (Jan. 5, 2001) Vol. 66(4):1092-1099.

[6] *Brenner v. Manson* 86 S.Ct. 1033, 383 U.S. 519 (1966).

In the Office Action, the Examiner again argues that the claimed method has no patentable utility because neither the endogenous ligand nor the biological function of the claim-recited GPCR is apparent. The Examiner also argues that the claimed method has no patentable utility because there is no explicit link between the recited GPCR and a disease. The Examiner cites no case law, rule, guideline or any other evidence supporting such arguments. As provided for in the rules, the Examiner is requested to provide evidence or an affidavit of personal knowledge under 37 C.F.R. § 1.104(d)(2) as to why a GPCR's endogenous ligand or biological function must be known before a method that uses that GPCR has patentable utility.

Further, the Examiner also argues on page 6 of the Office Action that the use of compounds identified by the claimed method in the study, diagnosis and monitoring of Parkinson's disease is considered a "research utility" that is neither specific nor substantial.

The Applicants respectfully disagree because tools for studying and monitoring diseases are frequently used in medicine and therefore have clear utility. Specifically at MPEP § 2107.01, Part I, the MPEP states:

> *Research Tools*
>
> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(underlining added by Applicants)

Moreover, the above-copied section of the MPEP dictates that "screening assays, and nucleotide sequence techniques have a clear, specific and unquestionable utility". Thus,

according to the MPEP, the showings that the Examiner appears to require in the Office Action do not appear to be necessary for a method of screening to be useful.

Since the instant claims are directed to a method of screening, and the MPEP states, in no uncertain words, that screening assays have a "clear, specific and unquestionable utility", the Applicants respectfully submit that the subject matter of the instant claims, must, too, have a clear, specific and unquestionable utility.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is requested.

REJECTIONS UNDER §112, ¶1 (ENABLEMENT)

Claims 5-8, 21-26 and 28-30 were rejected as not meeting the enablement requirement of 35 U.S.C. § 112, first paragraph. Claims 5-8, 21-26 and 28-30 have been cancelled and, as such, this rejection is moot with respect to those claims. To the extent that the Examiner believes that this rejection can be applied to new claims 31-45, this rejection is respectfully traversed.

The basis for this rejection is the Examiner's contention that the claims are not supported by a patentable utility.

As such, it is believed that this rejection has been adequately addressed in the discussion in the preceding section of this response.

In view of the discussion in the preceding section of this response, this rejection may be withdrawn.

REJECTIONS UNDER §112, ¶1 (WRITTEN DESCRIPTION)

Former claims 28-30 are rejected as not meeting the written description requirement of 35 U.S.C. § 112, first paragraph. Claims 28-30 have been cancelled and, as such, this rejection is moot with respect to those claims. To the extent that the Examiner believes that this rejection can be applied to new claims 31-45, this rejection is respectfully traversed.

The claims have been amended to recite a GPCR that is "encoded by a nucleic acid capable of hybridizing under stringent conditions to the complement of the nucleotide sequence of SEQ ID NO:19, wherein said stringent conditions comprise a wash in 0.1 X SSC at 65 °C and wherein said GPCR is constitutively active". Thus, the claims of this case require not only a nucleic acid capable of hybridizing under stringent conditions to a known sequence, but also that

the nucleic acid encodes an active GPCR, i.e., a GPCR that is "constitutively active". Moreover, the Applicants submit that a person of ordinary skill in the art at the time of filing would have known how to identify said G protein-coupled receptor as constitutively active in the absence of further analysis of the hARE-2 protein or gene, such as by using a GTPγS assay as described at page 11, lines 1-15 of the originally-filed application. It is believed the outstanding rejection has been addressed by the provision of new claims.

Further, the Court of Appeals of the Federal Circuit has addressed the issue of what constitutes adequate written description of claims that recite biological molecules in *Enzo*.[7] According to *Enzo*, "[a]dequate written description may be present for a genus of nucleic acids based on their hybridization properties, 'if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.'" *Enzo Biochem, Inc.*, 296 F.3d at 1327.

Given that claims of this case recite a genus of nucleic acids that remain hybridized to a known sequence (i.e., SEQ ID NO:19) under highly stringent conditions (i.e., a wash in 0.1 X SSC at 65 °C), the Applicants believe that *Enzo* applies and adequate written description should be found. In other words, following *Enzo*'s guidance, the genus of nucleic acids recited in the rejected claims are structurally similar and, as such, are adequately described.

The Applicants submit that this rejection has been adequately addressed by the foregoing discussion. Withdrawal of this rejection is requested.

REJECTIONS UNDER §112, ¶2

Former claims 5-8, 21-26 and 28-30 are rejected as not meeting the written description requirement of 35 U.S.C. § 112, second paragraph. Claims 5-8, 21-26 and 28-30 have been cancelled and, as such, this rejection is moot with respect to those claims. To the extent that the Examiner believes that this rejection can be applied to new claims 31-45, this rejection is respectfully traversed.

Specifically, the Examiner alleges that the claims are indefinite because: (1) the phrase "measuring the ability of the compound or compounds to inhibit or stimulate said receptor" is unclear; (2) the phrase "identifying the compound or compounds that inhibit or stimulate said

[7] *Enzo Biochem, Inc.*, 296 F.3d at 1327.

receptor as an agonist, partial agonist, or inverse agonist of said receptor" is unclear; (3) the phrase "an endogenous version" is unclear; and (4) it is unclear which hybridization conditions are used.

It is believed that this rejection has been largely addressed by the provision of a new set of claims. Specifically, the claims have been amended to remove the phrases in question.

The Applicants submit that there is no indefiniteness in the scope of the genus of nucleic acids recited in the claims because the recited wash conditions (0.1 X SSC at 65 °C) necessarily retain only nucleic acids that bind under high stringency. In other words, regardless of whether the recited wash is preceded by a low stringency hybridization or a high stringency hybridization, the wash will yield only those nucleic acids that remain bound under highly stringent conditions. Thus, while hybridization conditions are not explicitly recited in the claims, the claims are nevertheless clear because only nucleic acids that remain bound to SEQ ID NO:19 under defined stringency conditions are used.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of these rejections is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Director is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-011CON.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: April 17, 2008

By: /James S. Keddie, Reg. No. 48,920/
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Enclosures: IDS to cite Damier 1999A, Damier 1999B.

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